```
                 Hydrophobic                                    Hydrophilic
                    -2          -1           0           1           2
                 ----|---------|---------  |  --------|---------|-----
    1   -1.08                   ==========  M
    2   -1.28                 =============  S
    3   -1.74             ================  L
    4   -1.85            =================  F
    5   -2.11         ====================  g
    6   -1.61              ==============  L
    7   -1.50               =============  L
    8   -1.50               =============  L
    9   -1.28                 ===========  L
   10   -0.98                   =========  t
   11   -0.38                       ====  S
   12    0.07                          A  =
   13    0.18                          L  ==
   14    0.48                          A  =====
   15    0.50                          G  =====
   16    0.53                          Q  =====
   17    0.42                          R  ====
   18    0.42                          Q  ====
   19    0.43                          G  ====
   20    0.47                          T  =====
   21    0.23                          Q  ==
   22    0.25                          A  ===
   23    0.38                          E  ====
   24    0.38                          S  ====
   25   -0.08                       =  N
   26   -0.08                       =  L
   27   -0.20                      ==  S
   28   -0.20                      ==  S
   29   -0.20                      ==  K
   30   -0.67                  ======  F
   31    0.25                          Q  ===
   32    0.72                          F  =======
   33    1.17                          S  ============
   34    1.15                          S  ============
   35    1.10                          N  ==========
   36    0.82                          K  =======
   37    0.35                          E  ====
   38    0.35                          Q  ====
   39    0.32                          N  ===
   40    0.32                          G  ===
   41    0.63                          V  ======
   42    1.38                          Q  ==============
   43    1.85                          D  ==================
   44    1.05                          P  ==========
   45    0.75                          Q  =======
   46    0.15                          h  ==
   47   -0.42                       ====  E
   48   -0.87                  ========  R
   49   -1.43              ==============  I
```

Fig. 1

```
 50   -1.10       ===========  I
 51   -0.80         ========   t
 52   -0.18               ==   V
 53   -0.23               ==   S
 54   -0.37             ====   T
 55   -0.25              ===   N
 56   -0.28              ===   G
 57    0.22                    S ==
 58   -0.25              ===   I
 59    0.05                    H
 60    0.05                    S
 61   -0.07                =   P
 62   -0.05                    R
 63   -0.55           ======   F
 64    0.37                    P ====
 65    0.40                    H ====
 66    0.42                    T ====
 67    0.23                    Y ==
 68   -0.08                =   P
 69   -0.33             ===    R
 70   -1.40     ===============  N
 71   -0.93         ========   T
 72   -1.17     ============   V
 73   -1.17     ============   L
 74   -0.95        =========  V
 75   -0.95       ==========  W
 76    0.12                    R =
 77    0.12                    L =
 78    0.45                    V =====
 79    0.45                    A ====
 80   -0.03                    V
 81   -0.08                =   E
 82   -0.55           ======   E
 83   -1.35     ==============  N
 84   -1.45     ==============  V
 85   -1.62   ================  W
 86   -0.55           ======   I
 87    0.25                    Q ===
 88    0.72                    L =======
 89    0.60                    T ======
 90    0.67                    F ======
 91    0.78                    D =======
 92    0.78                    E =======
 93    0.78                    R =======
 94    0.28                    F ===
 95    1.20                    G ===========
 96    1.70                    L =================
 97    2.50                    E =======================
 98    1.70                    D =================
 99    1.03                    P =========
100    1.53                    E ==============
101    0.65                    D ======
102    0.65                    D ======
103   -0.27              ===   I
104   -0.22               ==   C
105    0.45                    K =====
```
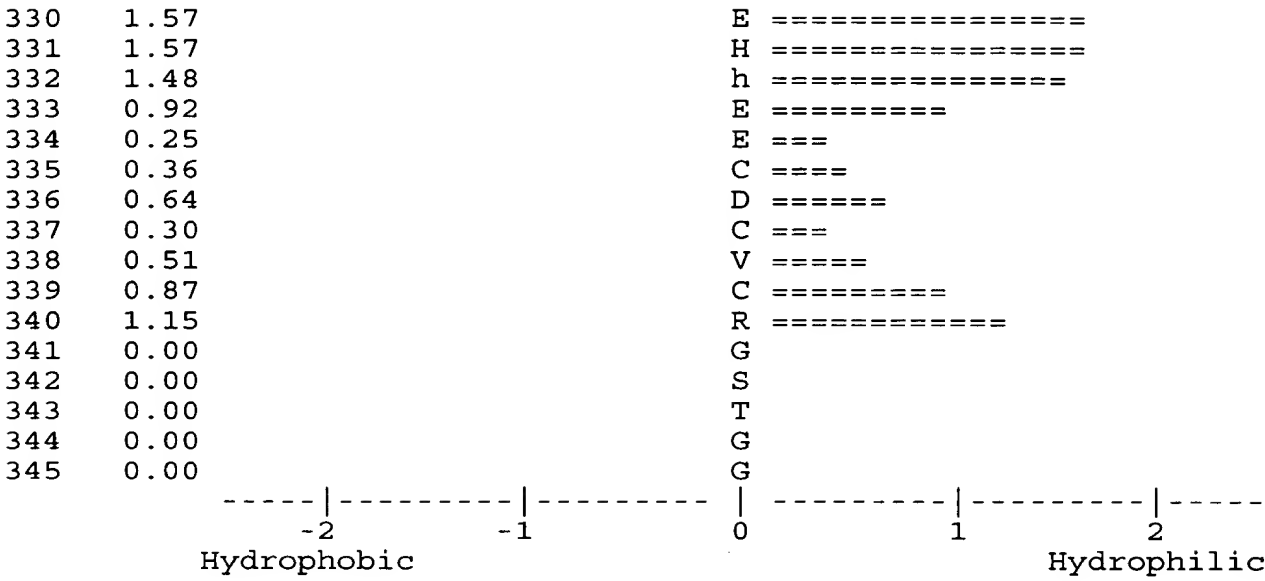
```
106   -0.30                                            ===  Y
107    0.58                                                 D  ======
108    0.58                                                 F  ======
109    1.00                                                 V  ==========
110    1.30                                                 E  =============
111    1.30                                                 V  =============
112    1.55                                                 E  ================
113    0.98                                                 E  ==========
114    0.18                                                 P  ==
115   -0.12                                              =  S
116   -0.17                                             ==  D
117   -0.17                                             ==  G
118   -0.73                                       =======  T
119   -0.83                                      ========  I
120   -0.53                                        =====  L
121   -0.80                                      ========  G
122   -0.80                                      ========  R
123   -1.37                           =============== W
124   -1.05                              ============ C
125   -0.88                                     ========= G
126   -0.88                                     ========= s
127    0.18                                                 G  ==
128    0.22                                                 T  ==
129   -0.02                                                 V
130    0.28                                                 P  ===
131    0.78                                                 G  ========
132    0.78                                                 K  ========
133    0.32                                                 Q  ===
134    0.32                                                 I  ===
135    0.32                                                 S  ===
136    0.77                                                 K  ========
137   -0.03                                                 G
138    0.47                                                 N  =====
139    0.02                                                 Q
140   -0.27                                            ===  I
141    0.08                                                 R  =
142    0.08                                                 I  =
143    0.88                                                 R  =========
144    0.00                                                 F
145    0.00                                                 V
146    0.25                                                 S  ===
147    0.25                                                 D  ===
148    0.25                                                 E  ===
149   -0.25                                            ===  Y
150    0.13                                                 F  =
151    0.13                                                 P  =
152   -0.03                                                 S
153   -0.38                                           ====  E
154   -0.97                                    ==========  P
155   -1.35                            ================= G
156   -1.32                             ================ F
157   -1.20                               ============== C
158   -1.28                              =============== I
159   -1.20                               ============== H
160   -1.12                                ============  Y
161   -0.70                                      ======  N
```

```
162   -1.15            ============= I
163   -0.92              ========= V
164   -0.17                    == M
165   -0.03                       P
166   -0.28                   === Q
167   -0.27                   === F
168    0.15                       T =
169    0.27                       E ===
170   -0.48                 ===== A
171   -0.70               ======= V
172   -0.45                  ==== S
173   -0.50                 ===== P
174   -0.45                  ==== S
175   -0.58                ====== V
176   -0.63                ====== L
177   -0.33                   === P
178   -0.63                ====== P
179   -0.13                     = S
180   -0.48                 ===== A
181   -0.70               ======= L
182   -0.37                  ==== P
183   -0.33                   === L
184   -0.12                     = D
185   -0.92              ========= L
186   -1.18            ============ L
187   -0.97             ========== N
188   -1.42           ============== N
189   -2.02       ==================== A
190   -2.00       ==================== I
191   -2.00       ==================== t
192   -0.93             ========= A
193   -0.35                  ==== F
194   -0.23                    == s
195    0.03                       T
196    0.60                       L ======
197    0.52                       E =====
198   -0.28                   === D
199   -0.28                   === L
200    0.02                       I
201    0.82                       R ========
202    0.82                       Y ========
203    1.03                       L ==========
204    1.37                       E ==============
205    0.57                       P ======
206    1.07                       E ===========
207    0.27                       R ===
208    0.27                       w ===
209    0.93                       Q =========
210    0.60                       L ======
211    0.52                       D =====
212    0.52                       L =====
213    0.82                       E ========
214    0.25                       D ===
215   -0.42                  ==== L
216   -0.08                     = Y
217    0.00                       R
```

```
218  -0.80                    ========  P
219  -0.80                    ========  T
220  -0.23                          ==  w
221  -0.15                           =  Q
222  -0.60                      ======  L
223  -0.55                      ======  L
224  -0.67                     =======  G
225  -0.67                     =======  K
226  -0.67                     =======  A
227  -0.08                           =  F
228   0.38                           V  ====
229   1.13                           F  ===========
230   1.30                           G  =============
231   1.05                           R  ===========
232   1.05                           K  ===========
233   0.25                           S  ===
234   0.23                           R  ==
235  -0.57                      ======  V
236  -0.62                      ======  V
237  -0.43                        ====  D
238  -0.43                        ====  L
239   0.37                           N  ====
240   0.08                           L  =
241   0.88                           L  =========
242   0.88                           T  =========
243   0.57                           E  ======
244   0.12                           E  =
245  -0.55                      ======  V
246  -0.37                        ====  R
247  -0.87                    =========  L
248  -0.07                           =  Y
249   0.35                           S  ====
250  -0.12                           =  C
251   0.10                           T  =
252  -0.08                           =  P
253  -0.03                           R
254  -0.83                    ========  N
255  -0.37                        ====  F
256   0.55                           S  ======
257   1.00                           V  ==========
258   0.95                           S  ==========
259   1.40                           I  ==============
260   2.20                           R  =======================
261   1.63                           E  =================
262   1.63                           E  =================
263   1.07                           L  ===========
264   1.07                           K  ===========
265   0.15                           R  =
266  -0.92                   =========  T
267  -0.85                    ========  D
268  -1.35               ==============  T
269  -1.45              ===============  I
270  -1.45              ==============  F
271  -1.33               =============  W
272  -1.02                  ==========  P
273  -0.52                       =====  G
```

```
274   -0.02                                    C
275   -0.02                                    L
276    0.28                                    L  ===
277    0.58                                    V  ======
278    0.87                                    K  ========
279    0.20                                    R  ==
280   -0.38                              ====  C
281   -0.38                              ====  G
282   -0.55                            ======  G
283   -0.85                        ==========  N
284   -0.97                      ============  C
285   -0.77                        ==========  A
286   -0.85                        ==========  C
287   -0.65                          ========  C
288    0.02                                    L
289    0.15                                    H  ==
290    0.27                                    N  ===
291    0.07                                    C  =
292   -0.02                                    N
293   -0.05                                    E
294   -0.50                             =====  C
295    0.17                                    Q  ==
296   -0.12                                 =  C
297   -0.02                                    V
298    0.73                                    P  =======
299    1.23                                    S  =============
300    1.20                                    K  =============
301    0.62                                    V  ======
302    1.37                                    T  ==============
303    1.18                                    K  ============
304    0.38                                    K  ====
305   -0.08                                 =  Y
306   -0.40                              ====  H
307    0.18                                    E  ==
308   -0.32                               ===  V
309    0.43                                    L  ====
310    0.67                                    Q  ======
311    0.63                                    L  ======
312    0.68                                    R  ======
313    0.68                                    P  ======
314    0.68                                    K  ======
315   -0.12                                 =  T
316   -0.13                                 =  G
317    0.37                                    V  ====
318    0.67                                    R  ======
319   -0.13                                 =  G
320   -0.20                                ==  L
321    0.60                                    H  ======
322    0.43                                    K  ====
323   -0.15                                 =  S
324   -0.50                             =====  L
325    0.30                                    T  ===
326    0.28                                    D  ===
327    0.10                                    V  =
328    0.85                                    A  ========
329    1.43                                    L  ==============
```

```
330   1.57                    E  ================
331   1.57                    H  ================
332   1.48                    h  ===============
333   0.92                    E  =========
334   0.25                    E  ===
335   0.36                    C  ====
336   0.64                    D  ======
337   0.30                    C  ===
338   0.51                    V  =====
339   0.87                    C  ========
340   1.15                    R  ===========
341   0.00                    G
342   0.00                    S
343   0.00                    T
344   0.00                    G
345   0.00                    G
              ----- | --------- | --------- | --------- | --------- | -----
                   -2          -1           0           1           2
              Hydrophobic                                      Hydrophilic
```

MT-1
PROMOTER

FseI
PmeI
AscI

hGH
polyA

RAT INSULIN II
INTRON

10 kB MT-1 5'
FLANKING REGION

7 kB MT-1 3'
FLANKING REGION

≈21 kB
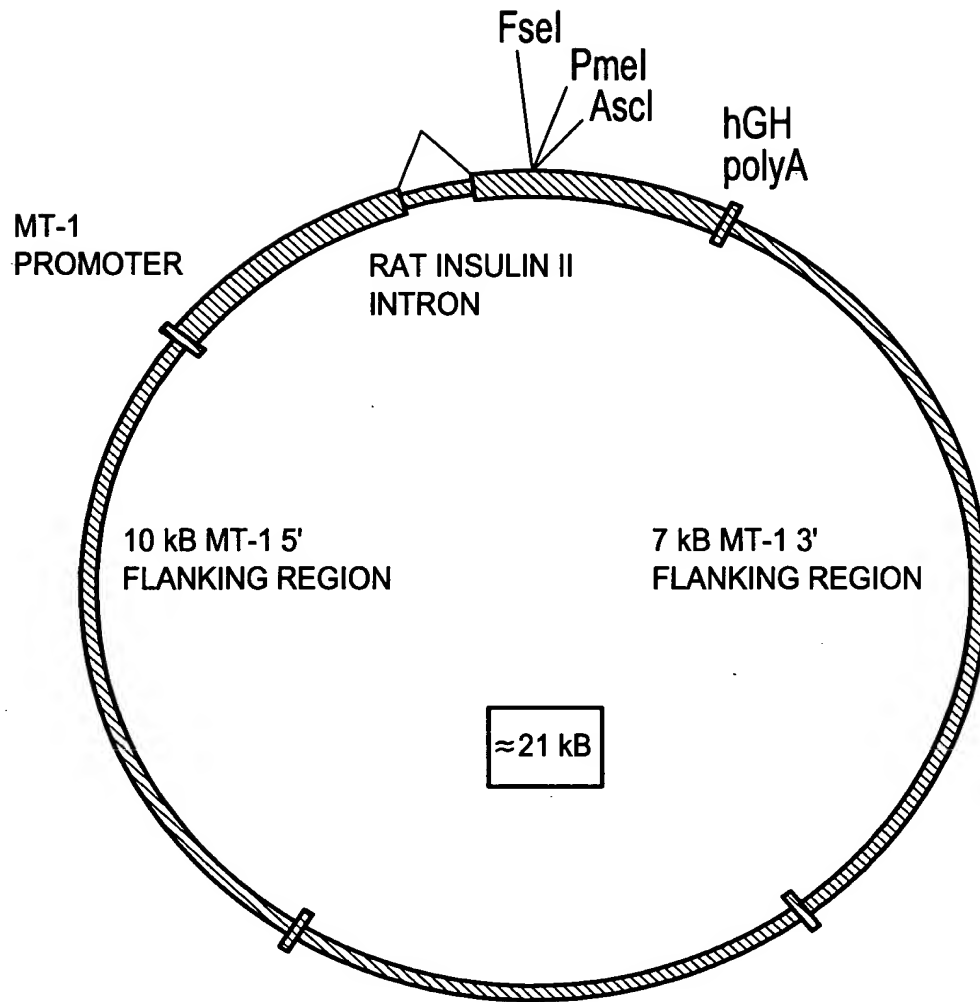
Fig. 2
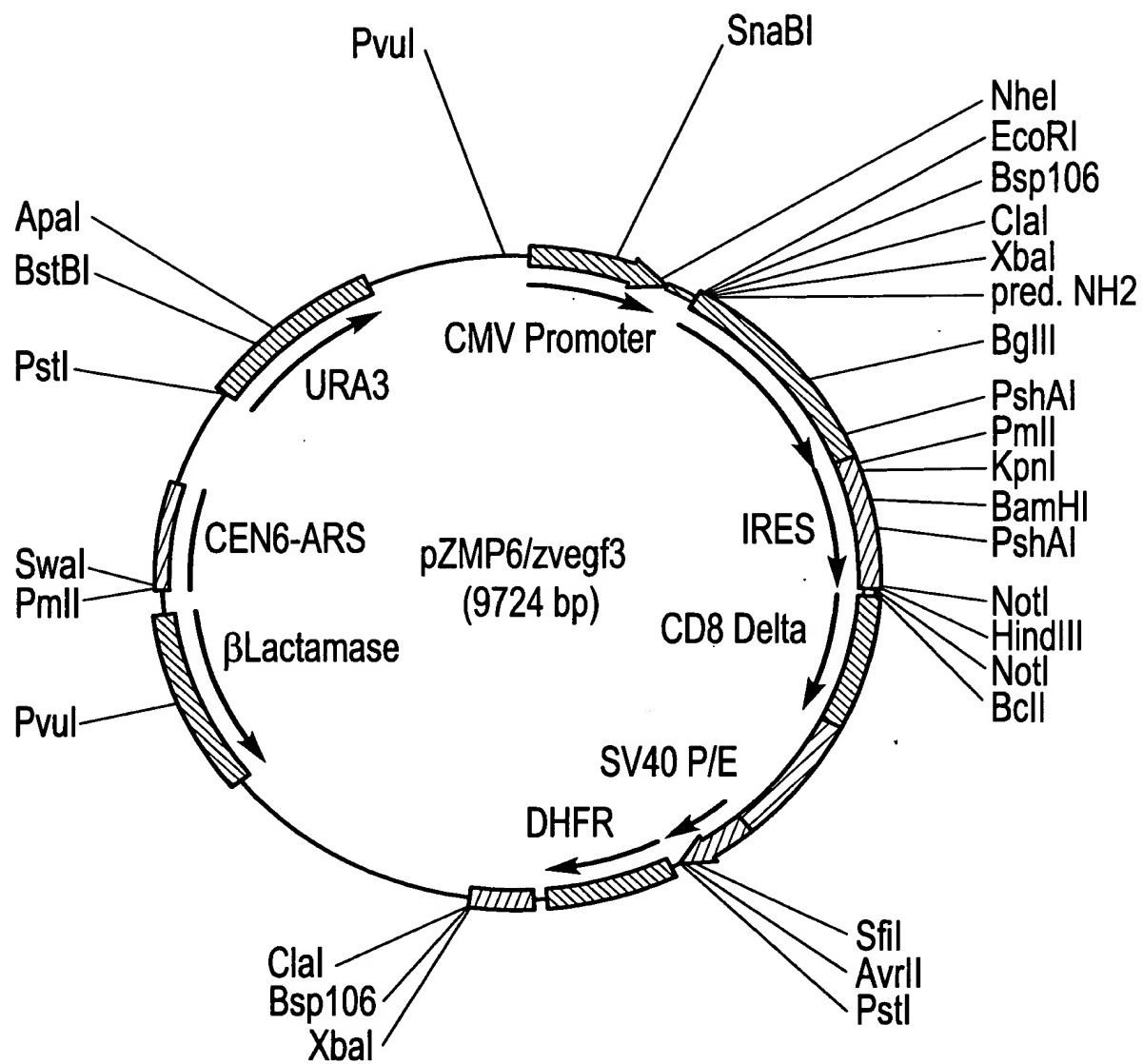
Fig. 3
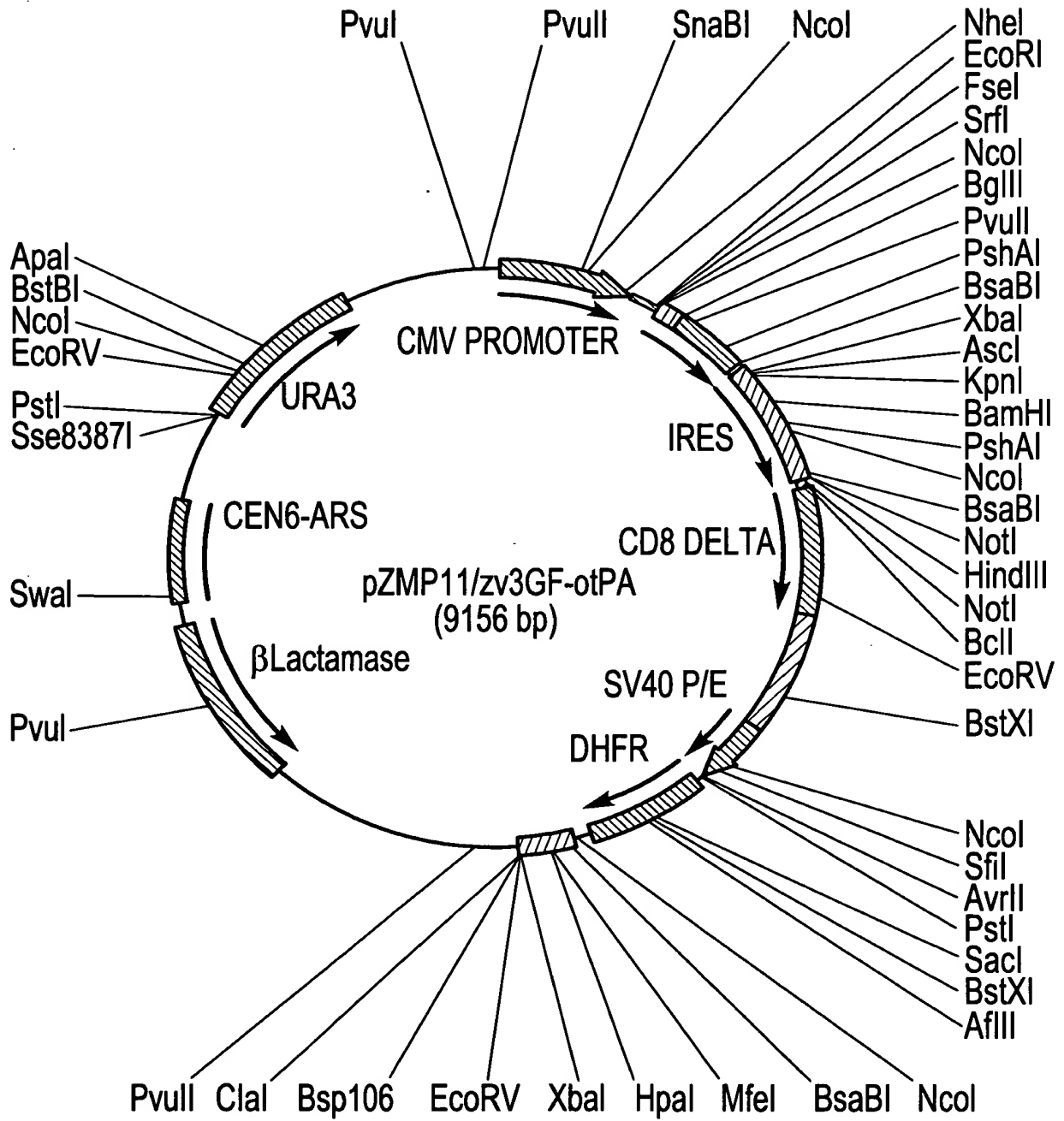
Fig. 4
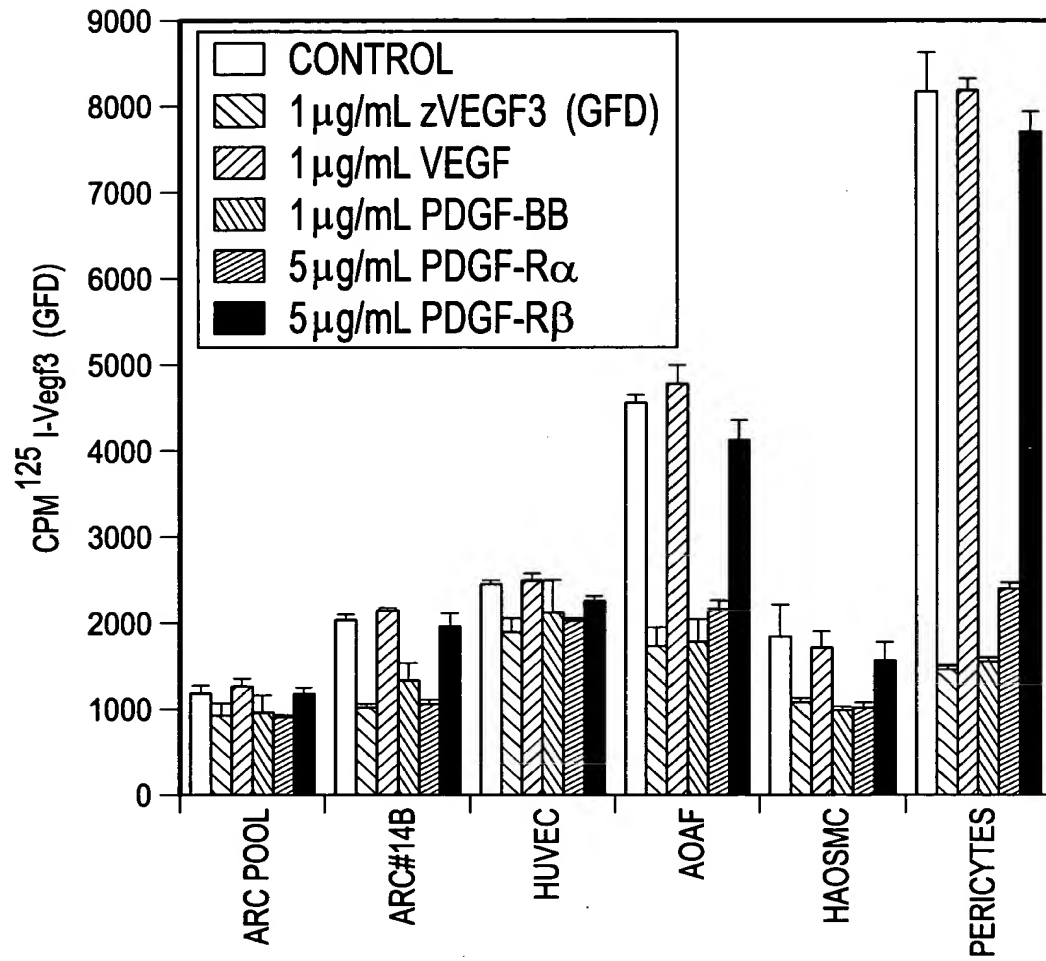
Fig. 5

MSLFGLLLLLTSALAGQRQGTQAESNLSSKFQFSSNKEQNGVQDPQHERIITVSTNGSIHS

MLLLGLLLLLTSALAGQRTGTRAESNLSSKLQLSSDKEQNGVQDPRHERVVTISGNGSIHS
     10   20   30   40   50   60

PRFPHTYPRNTVLVWRLVAVEENVWIQLTFDERFGLEDPEDDICKYDFVEVEEPSDGTIL

PKFPHTYPRNMVLVWRLVAVDENVRIQLTFDERFGLEDPEDDICKYDFVEVEEPSDGSVL
     70   80   90   100   110   120

GRWCGSGTVPGKQISKGNQIRIRFVSDEYFPSEPGFCIHYNIVMPQFTEAVSPSVLPPSA

GRWCGSGTVPGKQTSKGNHIRIRFVSDEYFPSEPGFCIHYSIIMPQVTETTSPSVLPPSS
    130   140   150   160   170   180

LPLDLLNNAITAFSTLEDLIRYLEPERWQLDLEDLYRPTWQLLGKAFVFGRKSRVVDLNL

LSLDLLNNAVTAFSTLEELIRYLEPDRWQVDLDSLYKPTWQLLGKAFLYGKKSKVVNLNL
    190   200   210   220   230   240

LTEEVRLYSCTPRNFSVSIREELKRTDTIFWPGCLLVKRCGGNCACCLHNCNECQCVPSK

LKEEVKLYSCTPRNFSVSIREELKRTDTIFWPGCLLVKRCGGNCACCLHNCNECQCVPRK
    250   260   270   280   290   300

VTKKYHEVLQLRPKTGVRGLHKSLTDVALEHHEECDCVCRGSTGG (SEQ ID NO:2)

VTKKYHEVLQLRPKTGVKGLHKSLTDVALEHHEECDCVCRGNAGG (SEQ ID NO:43)
    310   320   330   340

Fig. 6